ESTIMATION OF THE DEPROTECTION OF PHENOLS USING 2,4-DINITRO-1-FLUOROBENZENE USING ^{1}H NMR

A

Thesis submitted

in partial fulfillment of the requirement of degree of

Master of Science

in

Chemistry

Under the Supervision of

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Submitted by

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DEDICATED TO MY PARENTS

Acknowledgement

I am using this opportunity to express my gratitude to everyone who supported me throughout the course of this M.Sc project.

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Lastly, I am grateful to the God for the good health and wellbeing that were necessary to complete this project.

Manpreet Aulakh

Manpreet Kaur Aulakh

Patiala
Date: 15-7-15

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entiteled "**Estimation of the Deprotection of Phenols using 2,4-dinitrofluorobenzene by H^1-NMR**" for the partial fulfillment of the requirements of the award degree of Master of Science in Chemistry done at School of Chemistry and Biochemistry (SCBC), Thapar University, Patiala, is my own and during the period Jauary 2015 to May 2015, under the supervisor of Dr. Manmohan Chhibber, Associate Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this dissertation for the award of any other degree.

Manpreet Aulakh.

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This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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Certificate

This is to certify that the project entitled "**Estimation of the Deprotection of Phenols using 2,4-dinitrofluorobenzene by H^1-NMR**", being submitted by Ms. Manpreet Kaur Aulakh in partial fulfillment of the requirement for the award of degree of Master of Science in Chemistry done at School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under the supervision of Dr. Manmohan Chhibber and that no part of this project has been submitted for the award of any other degree.

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CONTENTS

INTRODUCTION

If under the given chemical conditions, two equally reactive or potent functional groups are present in a compound, it then becomes difficult to make one of them to react selectively while the other functional group remaining unaffected. The use of protecting groups thus, comes to the rescue of an organic chemist. Though it may add few extra steps to the synthetic procedure but is an effective synthetic tool which allows even such functional groups to react which normally remain inaccessible in the presence of other reactive functional groups. Protecting groups [1] are used in synthesis to momentarily mask a particular functional group because it may chemically interact with the other constituents of the reaction. A good protecting group should be easy to put as well as easy to remove and must show inert behavior to the given reaction conditions. It plays a crucial role in almost all the components of synthetic chemistry.

In organic chemistry, phenols are one of very reactive molecules. They are more acidic as compared to alcohols having pKa more than 10. The later have pKa in the range of 16 – 20. There are a number of molecules, both natural and synthetic those are derivatives of phenol. Some of such molecules have been shown in **Figure-1**. Therefore, protection of phenolic –OH group plays an important part for the synthesis of such molecules. Although a number of methodologies are known for the protection of phenols[1], the work presented here attempts to makes use of very convenient conditions for the protection and deprotection of phenols. While the protection was done using Sanger's reagent, deprotection required use of aliphatic primary amines.

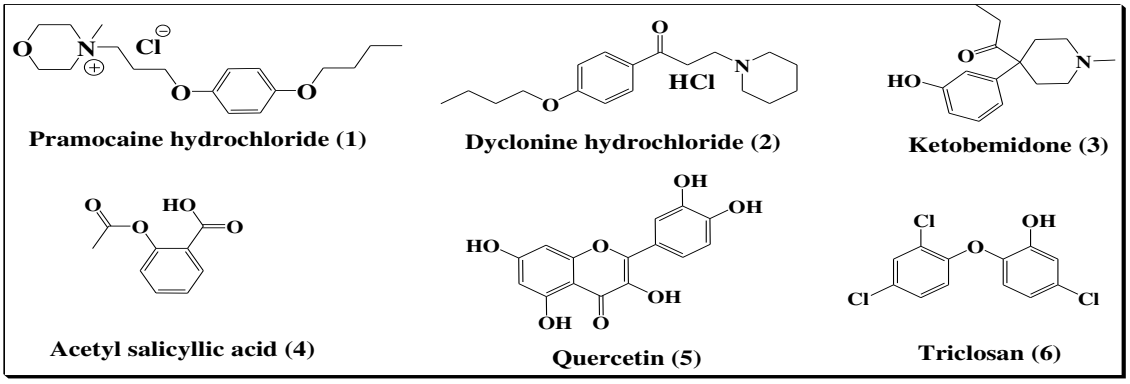


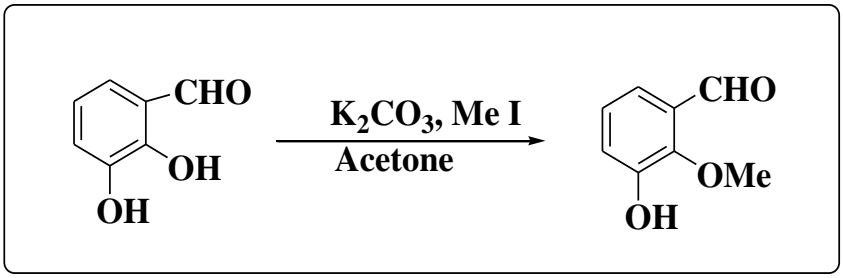
Figure -1 : Commercially available molecules that contain phenols or its derivatives

REVIEW OF LITERATURE

Selective protection and deprotection of functional groups is one of the most important approaches in multistep organic synthesis. Main focus of the present work is protection and deprotection of the hydroxy group of the phenols. The literature presented here summarizes (a) conventional and recent reports on the protection of phenols and (b) Smiles rearrangement, the background of the methodology on which our scheme is based.

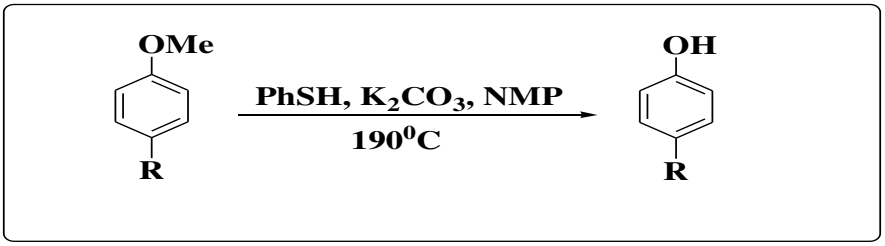
(a) Protection of phenols

Phenols get easily protected in the presence of methyl iodide and no strong bases are required. In the following case **(Scheme-1)**, ortho hydroxyl group is more acidic hence more reactive.[2] The starting phenol in the presence of potassium carbonate, methyl iodide and acetone was refluxed for about 6 hours.[3] This group can be removed very efficiently using BBr_3, a Lewis base.



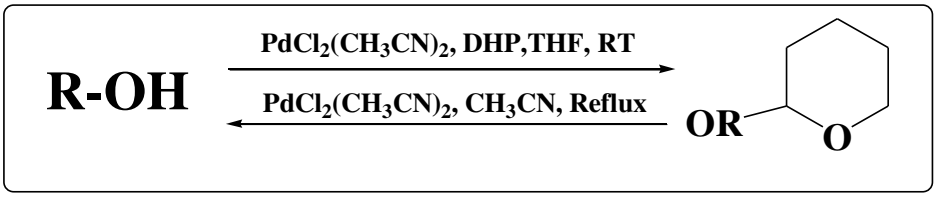
Scheme-1: Protection of -OH groups using methyl iodide

The deprotection approach has been improved **(Scheme-2)** which allows the use of only one equivalent of thiophenol in 1-methyl-2-pyrrolidone (NMP) with a catalytic amount (2–5 mol %) of potassium carbonate as a base. The reaction completes in 10-30 mintues.[4]



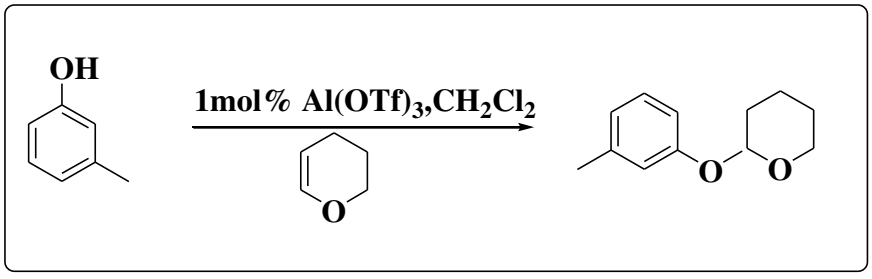
Scheme-2: Deprotection of phenol derivatives by thiophenol

Tetrahydropyran (THP) is also an extremely useful and versatile reagent for the protection of alcohols and phenols because of its low cost **(Scheme-3)**. This is stable to most non acidic reagents and can be easily removed. The tetrahydropyran (THP) group could be efficiently removed using 0.1eq. $PdCl_2(CH_3CN)_2$,a lewis acid catalyst, in CH_3CN keeping other protecting groups intact.[5]



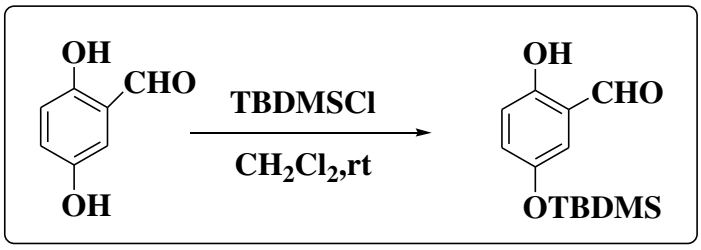
Scheme-3 : Protection and deprotection of alcohols using DHP

A recent improvement is use of aluminium triflate to convert alcohols and phenols to corresponding THP or THF ethers in good yield **(Scheme-4)**.The advantage of this method is use of same reagent, aluminium triflate, as a deprotecting catalyst in the presence of methanol at ambient temperatures.[6]



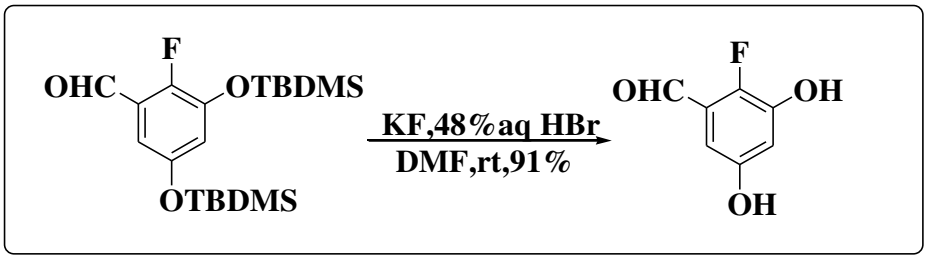
Scheme-4: Protection of phenols by $Al(OTf)_3$

t-Butyldimethylsilyl ether (TBDMS or TBS ether) is also one of very widely used protecting groups in alcohol chemistry that can be easily cleaved as well **(Scheme-5)**. Protection produces product with quantative yields.[7]



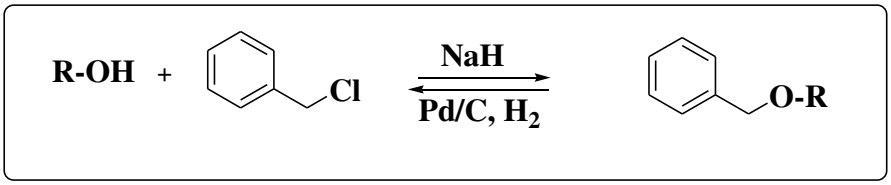
Scheme-5: Protection of phenols using TBDMS

TBDMS group after protection can be easily removed by adding potassium fluoride and aqueous HBr to the reactants at room temperature in the presence of DMF **(Scheme-6)** [8]



Scheme-6: Deprotection of -OH group using HBr, KF

Benzyl chloride is often used as protecting reagents for alcohols and phenols in organic synthesis. Protection of benzyl group is normally carried out by treating alcohols with a benzyl halide in the presence of base, such as sodium hydride.[9] The debenzylation requires use of Pd over cabon and hydrogen gas to give back alcohol. This methodology is widely used in carbohydrate chemistry.

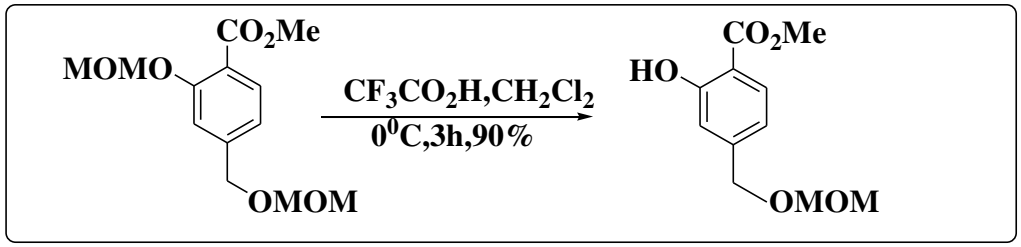


Scheme-7: Protection and deprotection using benzyl chloride

Methoxy methyl ether, normally abbreviated as MOM, is also used as a protecting group for a number of alcohols. It utilizes chloro alkyl ethers (MOMCl) with catalytic amount of potassium carbonate and acetone / DMF as a solvent for the protection of phenols. Chloro alkyl ethers have a general formula R-O-$(CH_2)_n$-Cl where ether is connected to a chloro methyl group via an alkane chain. Product yields are quantative in the protection step. This protection is used quite frequently but in some cases selectivity is based on effect of the neighboring groups. For example, in the following **Scheme-8** activity of the one of hydroxyls is reduced due to hydrogen bonding with neighboring carbonyl and results in the protection of other –OH group.[10,11]

Scheme 8: Protection of phenols with MOMCl

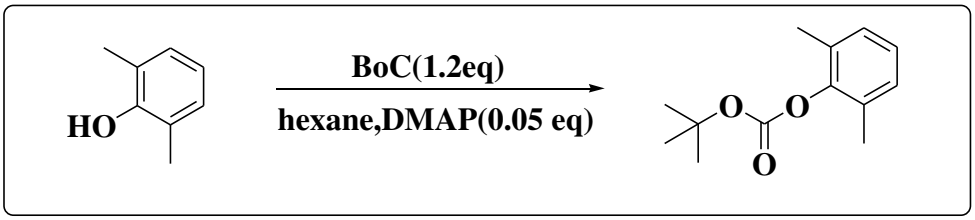
The cleavage of MOM- ether is a simple task. The method described in **Scheme -9** selectively cleaves phenolic MOM group only in the presence of triflouroacetic acid along with dichloromethane in refluxing conditions to give high yields.[12]



Scheme-9:Deprotection of phenols using trifluroacetic acid

Organic carbonates are very important compounds from pharmacological and chemical point of view.[13] A lot of functional groups are known to be used for the protection of a primary hydroxy group in presence of a secondary hydroxy group.[14] Due to steric crowding, introduction and removal of protecting groups on hindered phenols is difficult and requires drastic conditions. [15] Tert-Butoxycarbonyl (Boc) offers advantage of

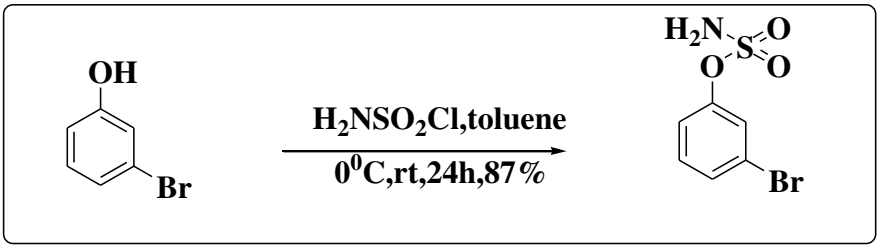
protecting even hindered groups due to high acidity and reactivity of phenols.[16] **Scheme –10** below shows that hindered phenol, as illustrated below, react quickly only in a slight excess of Boc_2O to afford complete conversion.[17]



Scheme-10: Protection of -OH using BoC

The cleavage in this case is simple where refluxing Boc protected compound in the presence of 3M HCl in dioxane affords the phenol.

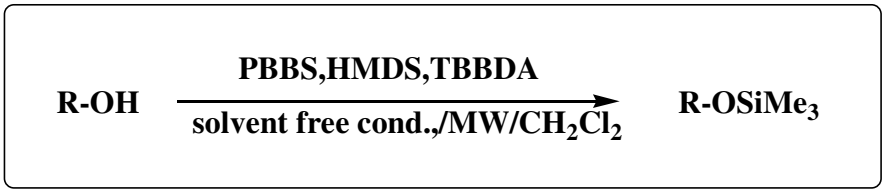
Sulfamates present another class of protecting groups that are used at the end of a multistep organic synthesis for the protection of phenols due to their labiality under basic conditions. Alcohols and phenols can be conveniently converted into the corresponding sulfamates ($ROSO_2NH_2$and $ArOSO_2NH_2$, respectively) by the direct reaction with sulfamoyl chloride (H_2NSO_2Cl) which in turn is prepared from chlorosulfonyl isocyanate and formic acid.[18] **Scheme-11** below shows a recent approach to protect hydroxyl in 3-bromophenol into corresponding sulfamate.[19]



Scheme-11: Protection of -OH group by sulfamoyl chloride

Silylation of phenols/alcohols is a frequently used protection method in multistep synthesis due to its enhanced stability under a variety of conditions and the ease of removal. The removal of silyl group is generally activated by use of acid/ base induced hydrolysis. It gives only siloxane as a by-product. Recently **(Scheme- 12)**, silylation of phenols/alcohols under solvent and solvent free conditions with conventional or

microwave irradiation has been respectively achieved in the presence of poly (N-bromobenzene-1,3-disulfonamide), PBBS, and N,N,N',N'-tetrabromobenzene-1,3-disulfonamide (TBBDA) with Hexamethyldisilazane (HMDS).[20] The later is a stable, cheap, and commercially available compound. Trimethylsilyl ethers are synthesised from hydroxy orthio compounds with it.

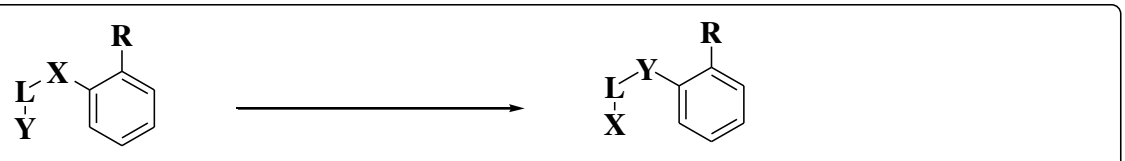


Scheme-12: Protection of alcohals using PBBS,HMDS

In fact, there are many more protecting groups like formacetal derivatives ($ROCH_2O$-) perfluoroaryl derivatives [21], allyl bromide and acetylimidazole [22] for the protection or selective protection of phenols. The work presented ahead uses very simple conditions and commercially available cheap reagents to carryout protection of phenols.

(b) Smiles Rearrangement

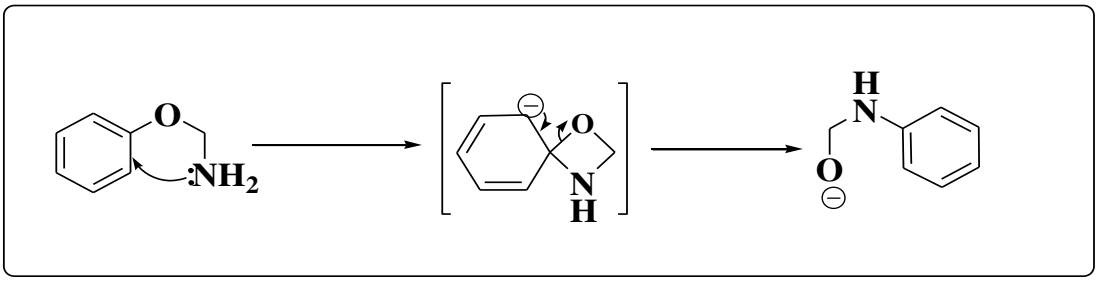
Smiles rearrangement is one of very useful methods for C-N bond formation to prepare N-aryl amines. The rearrangement has seen widespread use in organic chemistry.[23] Traditional, Smiles rearrangement requires the activation by the substituent in the migrating aryl unit as *ortho* or *para*-nitro groups. **Scheme -13** below shows a general reaction pathway for the formation of a Smiles rearrangement product. Such rearrangement is known to take place photochemically as well.[24]



where Y = -O,- S, -NR and X is usually -S, -SO, -SO_2, O or -COO and L is Linking unit.

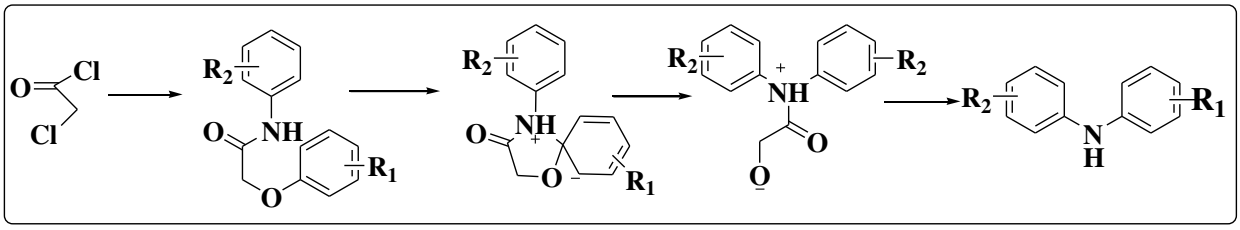
Scheme-13

The reaction proceeds by intramolecular nucleophilic aromatic substitution reaction as detailed in **Scheme-14**.



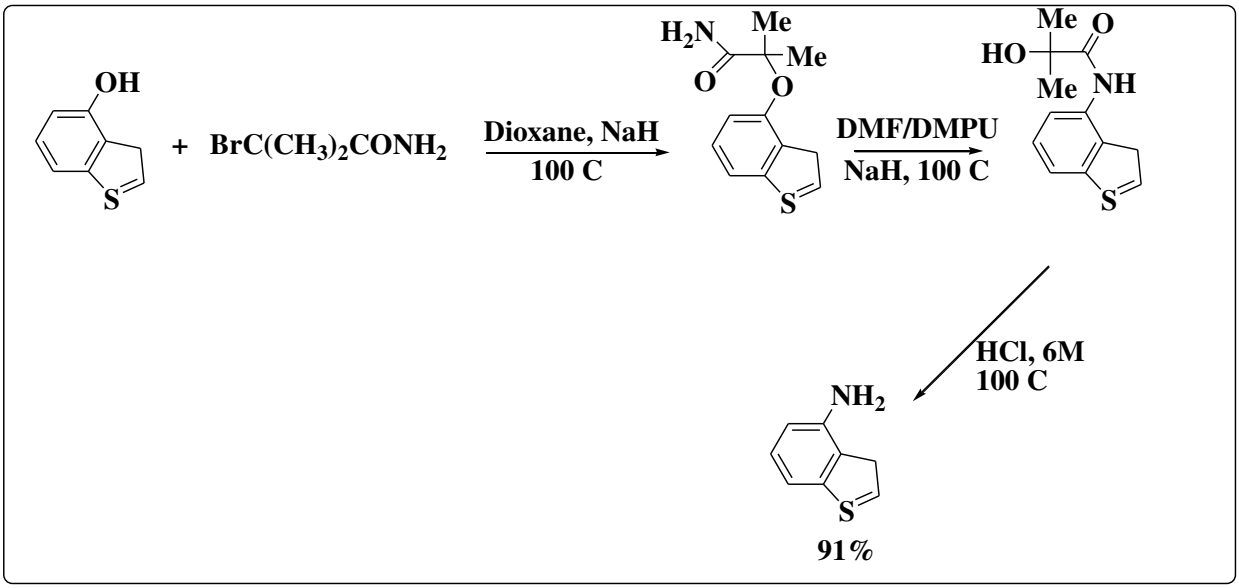
Scheme-14

A number of applications of this rearrangement have been developed in recent years. Tian and co-workers have develop a methodology for the synthesis of diphenyl amines using Smiles rearrangement using phenols and phenylamines in the presence of chloroacetyl chloride. **Scheme-15** below demonstrates the proposed mechanism of the reaction.[25]



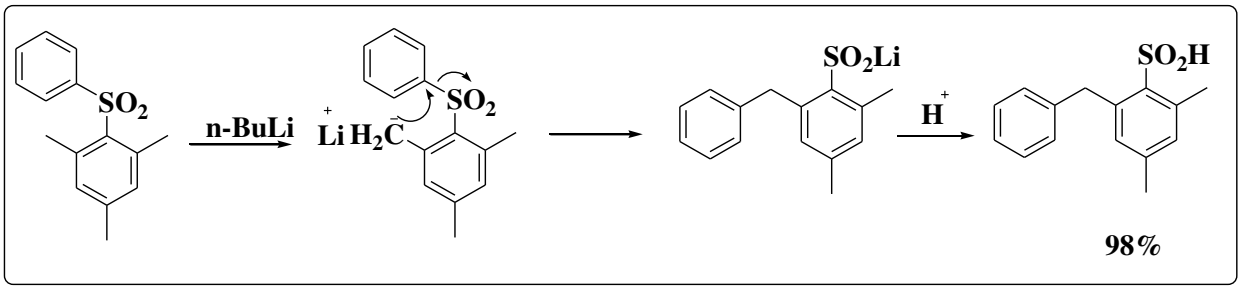
Scheme-15: Proposed mechanism for the formation of diarylamines via Smiles rearrangement

It has also been used for pharmaceutically important heterocyclic motifs like for the synthesis of 5-amino-substituted [1]benzothieno[2,3-b]pyridine **(Scheme – 16)** units by C. Bonini *et. al*.[26]



Scheme 16

In late fifties W. E. Truce developed a similar protocol where the nucleophile instead of being a heteroatom was shown to be a carbanion to give substituted aromatic sulfinic acids. This methodology is now known as Truce–Smiles rearrangement and is now well established.[27] It uses a strong base to deprotonate a methyl group that behaves similar to nucleophilic hetroatom as in conventional Smiles rearrangement. **Scheme-17** below demonstrates the mechanism of such a reaction.



Scheme 17

Present work makes use of a similar methodology to deprotect a phenol that is initially protected by 2,4-dinitrofluoro benzene to afford a diphenyl ether. The use of primary amine cleaves the diphenyl ether to give back phenol.

MATERIALS AND METHODS

All the reagents and solvents except amines were purchased from S.D Fine Chemicals, Mumbai. The amines used were procured from Aldrich. Petroleum ether and ethyl acetate and silica gel (60-120 mesh) were used in column chromatography for purification of diphenyl ethers. TLC analysis was done on glass plates which were coated by slurry made from silica in petroleum ether. ^{1}H NMR was done using $CDCl_3$ as solvent and tetramethyl silane (TMS) was used as an internal standard

Experimental Section

General procedure for the synthesis of diphenyl ethers: (For compounds A, 2a, 3a) 1-Flouro-2,4 dinitrobenzene (2.98mmol) and phenol (2.99mmol) were taken in a 100 ml round bottom flask and K_2CO_3 (2.99mmol) added. To this mixture was added DMF (10ml) and catalytic amount of 18-crown-6 and stirred for about 10 hrs at room temperature. TLC was done to monitor the progress of the reaction using petroleum ether and ethyl acetate in 70:30 ratio as a solvent. After completion of the reaction aqueous NaOH (0.1M) was added and the solid obtained was filtered. It was neutralized with 2% HCl followed by washing with water (4-5 times) to remove excess of solvent and pH was checked to 7 using pH paper. The crude product was dried using vacuum pump. All the diphenyl ethers were purified using column chromatography using pet ether and ethyl acetate in gradient increase in polarity.

4-(2,4-Ditrohenoxy)-3-methoxybenzaldehyde (1a) : ^{1}H NMR (400MHz, $CDCl_3$): δ 3.8(s, 3H), 6.9 (d, J= 9.2 Hz, 1H), 7.26(s, 1H), 7.38(d, J=8.72 Hz, 1H), 8.31(d, J=6.4 Hz, 1H), 10.0(s, 1H).

4-Allyl-1-(2,4-dinitrophenoxy)-2-methoxybenzene (2a) : ^{1}H NMR(400MHz, $CDCl_3$): δ 3.4(d, 2H), 3.74(s, 3H), 5.15(d,2H), 6(m, 1H), 6.87(d, 3H), 7.1(d, 1H), 8.26(d, 1H), 8.87(s, 1H).

3-(2,4-Dinitrophenoxy)phenol (3a) : ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.0 (brs, 1H), 6.6 (t, *J* = 2.3 Hz, 1H), 6.7 (dd, *J* = 10.5,2.7Hz, 1H), 6.8 (dd, *J* = 10.5,2.3Hz, 1H), 7.1 (d, *J* = 9.2Hz, 1H), 7.3 (t, *J* = 8.2 Hz, 1H), 8.3 (dd, *J*= 11.9, 2.7Hz, 1H), 8.8 (d, *J*=2.8 Hz, 1H).

Synthesis of 4-(2,4-Dintrophenoxy)-3-methoxybenzyl alcohol (1a)

Compound (A) (0.5g, 1.5mmol) was taken in 250 ml round bottom flask. To this was added sodium borohydride (0.028g, 0.75mmol) slowly and methanol (150 ml) was added. The reaction mixture was stirred for about 2-3 hrs at room temperature and TLC monitoring done. A new spot appeared which indicated that product had formed. Methanol was evaporated using rotary evaporator. Crude product obtained was purified by column chromatography using petroleum ether and ethyl acetate as solvents. Yellow colored solid was analyzed by ^{1}H NMR (400MHz, $CDCl_3$): δ 3.78(s, 3H), 4.75(s, 2H), 6.87(d, J=9.6 Hz, 1H),7.11(d, 1H), 7.17(d, J=8.2 Hz, 1H), 8.25(d, J=2.8, 1H), 8.28(s, 1H), 8.8(d, J=2.8, 1H).

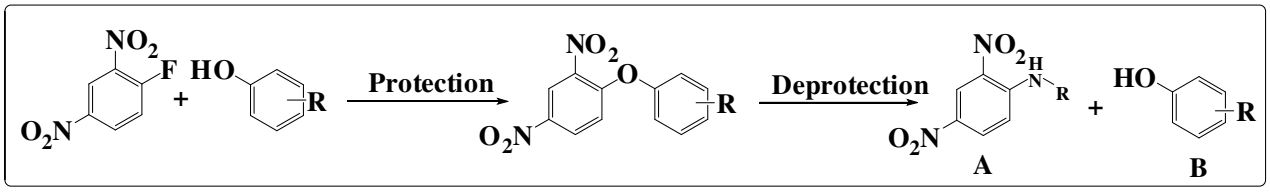
Synthesis of 3-methoxy-4-(2-nitrophenoxy)benzaldehyde (4a) : 1-Flouro-2-nitrobenzene (2.98mmol) and vanillin (2.99mmol) were taken in a 100 ml round bottom flask and K_2CO_3 (2.99mmol) added. To this mixture was added DMF (10ml) and catalytic amount of 18-crown-6 and stirred for about 10 hrs at room temperature. TLC was done to monitor the progress of the reaction using petroleum ether and ethyl acetate in 70:30 ratio as a solvent. After completion of the reaction it was taken in dichloromethane (25 ml) and washed with aqueous NaOH (0.1M 3X 20 ml) and neutralized with water (3 x 25 ML). Finally dichloromethane was evaporated and the crude product obtained was purified using column chromatography using using pet ether and ethyl acetate in gradient increase in polarity. The purified product was analyzed using 1H NMR (400MHz, $CDCl_3$): δ 3.91(s, 3H), 7.0(d, 1H), 7.05(d, 1H), 7.3(t, 1H), 7.46(d, 1H), 7.5(t, 1H), 8.0(d, 1H), 9.9(s, 1H).

General Procedure for the deprotection of Phenols: Compound **(1a - 4a)** (0.6mmol) was taken in 100 ml round bottom flask and methanol (10ml) along with octylamine (0.103 ml) was added. The reaction mixture was refluxed for about 2 hrs and TLC analysis was done to monitor the reaction. After 2 hrs methanol was completely evaporated using rotary evaporator and the crude product was analyzed using 1H NMR using $CDCl_3$ as solvent. Percentage conversion was done using formula as given as equation-1 (Result and Discussion).

RESULTS AND DISCUSSION

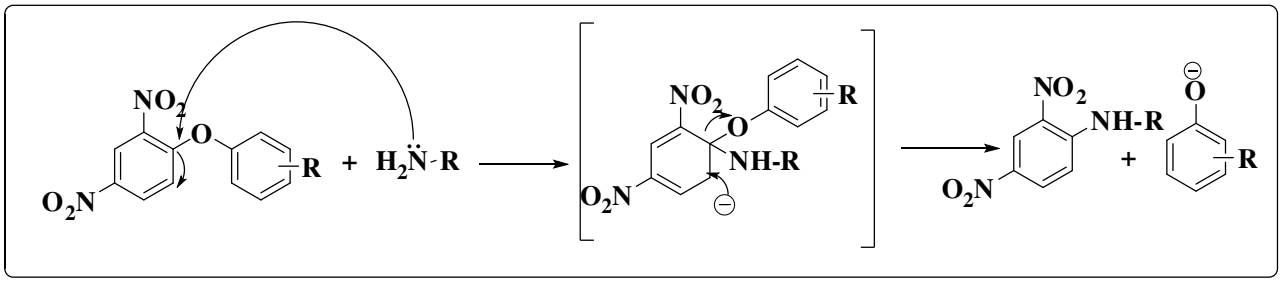
Phenol is one of very reactive groups in organic chemistry due to its high acidity. This reactivity interferes while carrying out reactions of the motif containing phenols. Therefore protection followed by deprotection of phenols becomes important. A number of methods for this are known and some of them have been discussed above. Here a convenient procedure for protection and deprotection of phenols has been described.

The protection of different phenols has been done using 2,4-dinitro fluorobenzene to give diphenyl ether that gets conveniently deprotected by heating it with primary amine , octyl amine in our case, in methanol **(Scheme –A)**.



Scheme- A

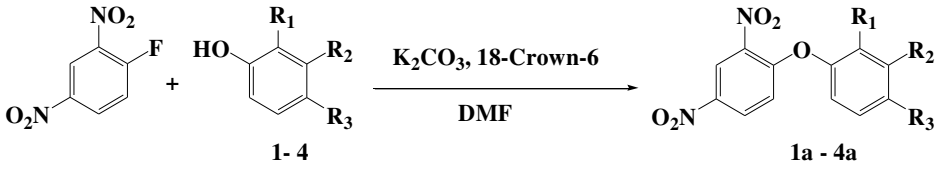
Here, both protection and deprotection steps proceed by nucleophilic aromatic substitution. While in the former case phenol acts as a nucleophile to give diphenyl ether, in the later case primary amine acts as a nucleophile. **Scheme –B** below describes the mechanism of deprotection which is very similar to Smiles rearrangement discussed above. While Smiles rearrangement is an intramolecular reaction, where the heteroatom acts as a nucleophile to attack electron deficient aromatic ring **(Scheme – 14)** in our case it's an intermolecular nucleophilic attack by primary amine on electron deficient aromatic ring.



Scheme - B

In the present work, five different phenols (**Compound 1**, **2**, **3** and **4**, **Table-1**) were protected using 2,4-dinitrofluorobenzene to get corresponding diphenyl ethers via

nucleophilic aromatic substitution reaction. The reaction was done in a protic solvent, DMF and mild base, K_2CO_3, and catalytic amount of 18-Crown-6. All the compounds were characterized by ^1H and ^{13}C NMR techniques.



1- 4 1a - 4a

S. No.	Compound No.	R_1	R_2	R_3	Product No	Reference Figure
1.	1	OCH_3	H	CH_2OH	1a*	Figure-1a
2.	2	OCH_3	H	$CH_2CH=CH_2$	2a	Figure-2a
3.	3	H	OH	H	3a	Figure-3a
4.	4**	OCH_3	H	CHO	4a	Figure-4a

***** Compound **1a** was synthesized from corresponding aldehyde . The aldehyde was reduced using $NaBH_4$ in MeOH.

** In case of **compound 4** only 2-nitofluorobenzene was used and hence corresponding product was obtained.

Each of the product obtained in above **Table -1** (Compounds **1a**, **2a**, **3a**, **4a**) was refluxed with one equivalent of octyl amine in presence of the solvent for one hour. TLC monitoring was done with **compound 5 (Figure-2),** used as a standard, to access the completion of the reaction. Generally the reaction was complete in an hour. Percentage conversion to corresponding phenol was done by ^1H NMR using the formula given by **Equation-1**.

Conversion (%) = 100 x $\mathbf{I_{Peak\ X} / I_{Peak\ X} + I_{Peak\ Y}}$ (Equation -1)

Where $\mathbf{I_{Peak\ X}}$ and $\mathbf{I_{Peak\ Y}}$ are the integrations due to proton X and proton Y in the reaction mixture of the compound as shown in **Figure - 2** below. The method of using ^1H NMR is a well established method and routinely used for the percentage conversion of biodiesel from oil[28].

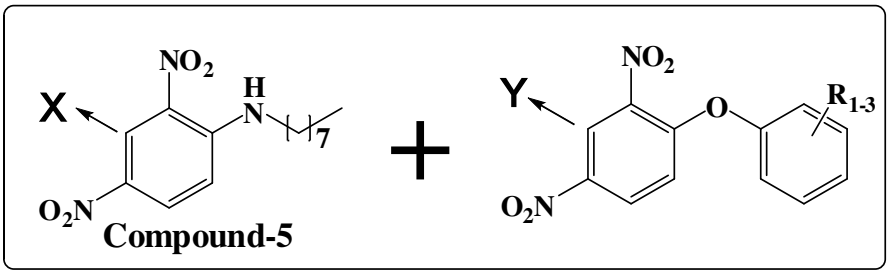


Figure-2

Compund-5 was used as marker to estimate the deprotection of the phenol. This is because phenyl octyl amine, **Compound -5**, will be obtained as the side product on lines similar to Smiles rearrangement as per proposed mechanism shown in **Scheme - B**. **Table-2** below summarizes the results of percentage conversion for deprotection of phenols.

Table-2

S.NO.	Product No.	Percentage Conversion	Reference Figure
1.	1a	75.59	Figure-3
2.	2a	83.18	Figure-4
3.	3a	100.00	Figure-5

Interestingly, it has been observed that compound **4a**** **(Table-1)** did not undergo deprotection of phenols. This compound unlike other compounds in **Table-1** has only one nitro group at the ortho position and therefore undergoes Schiff's base formation. NMR in **Figure – 6** shows a peak at 8.3 ppm due to Schiff's base as a result of reaction with its aldehyde. Our earlier results have shown that in the presence of two nitro groups and aldehyde the deprotection is a preferred reaction.[29] Thus it is evident that only 2, 4-dinitro group can act as a protecting group.

In conclusion, we have attempted to show that 2, 4-dinitro fluorobenzene can be conveniently used as a protecting group for phenols that can be conveniently deprotected using octyl amine in methanol.

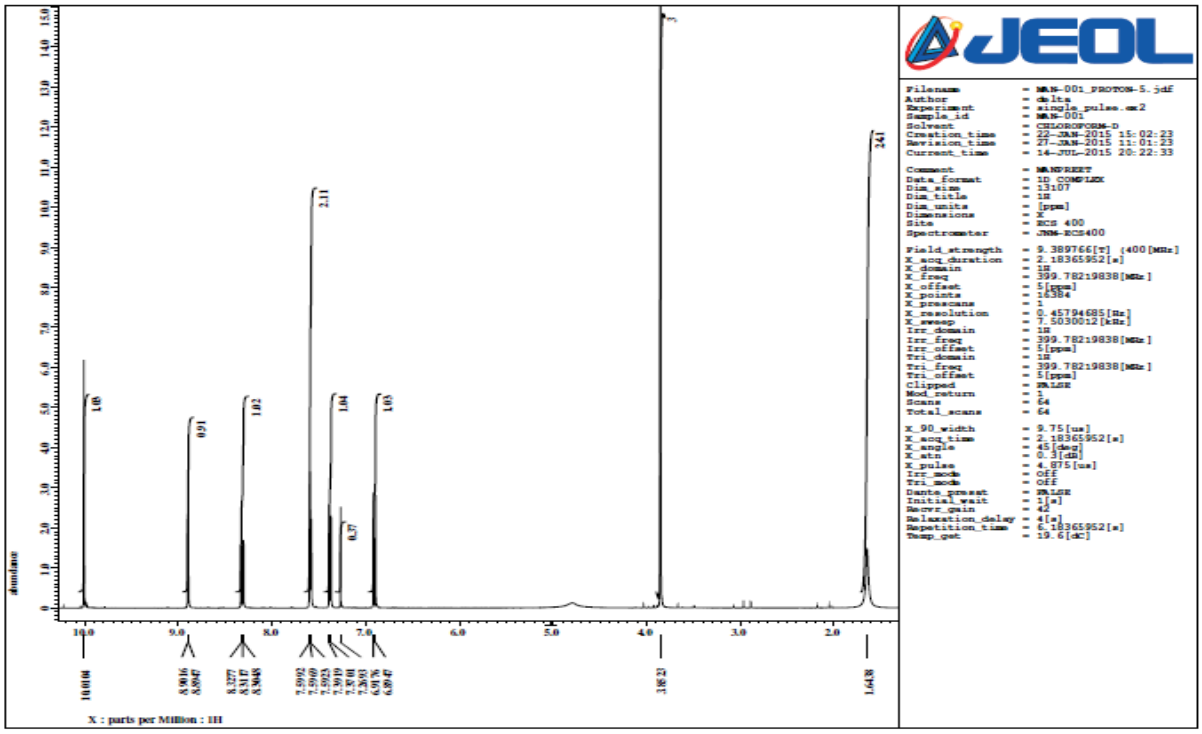


Figure 1A: Synthesis of compound A (H^1-NMR)

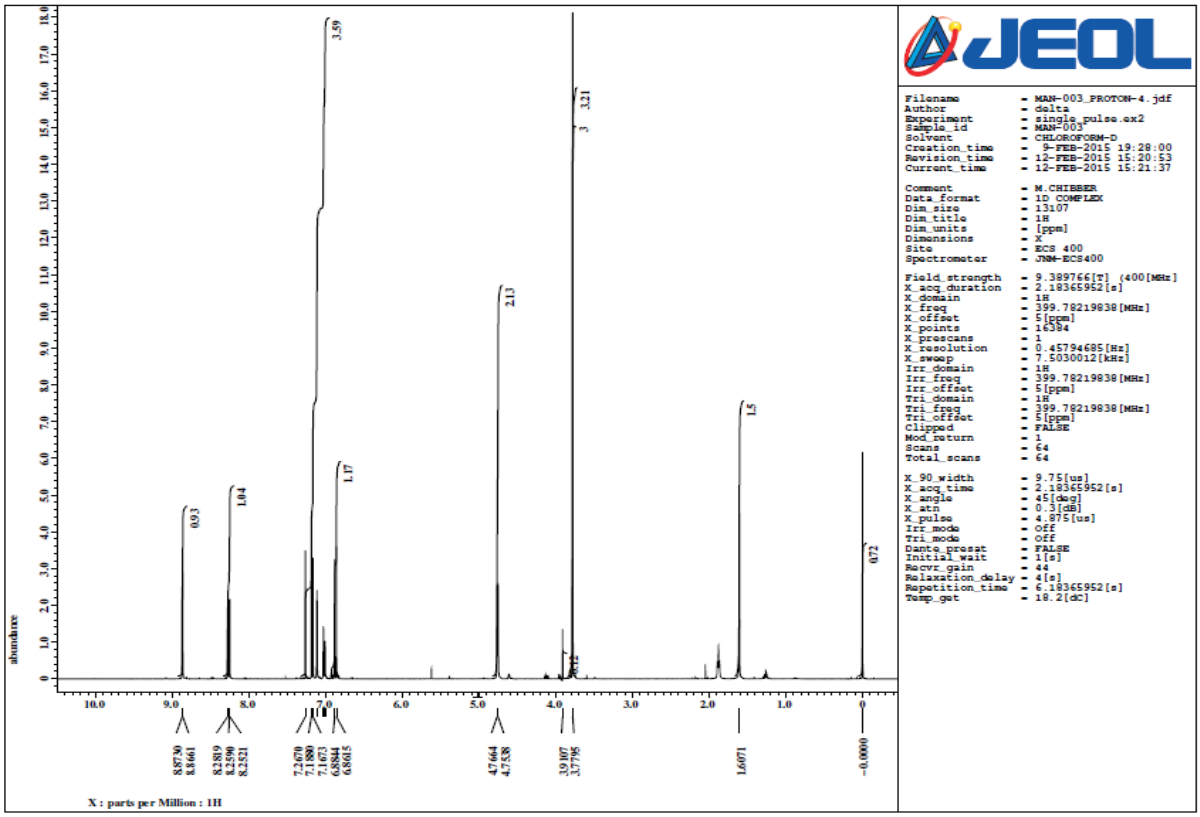


Figure 1a: Synthesis of compound 1a

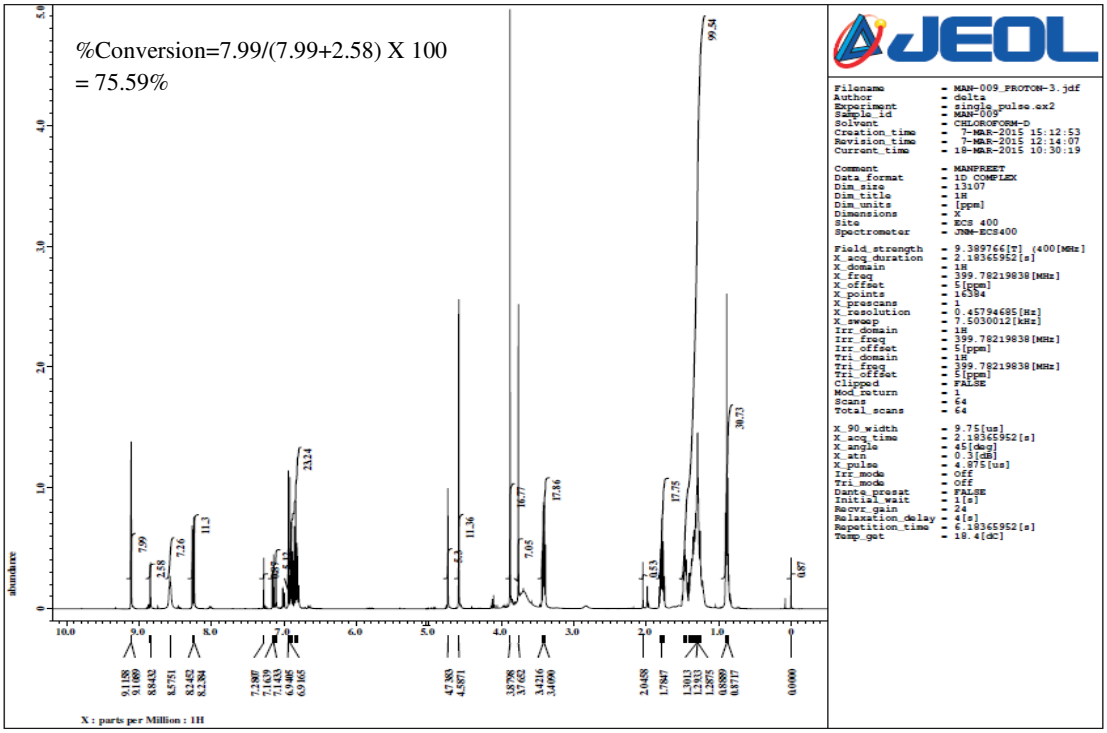


Figure 3: Deprotection of compound 1a using Octyl Amine (H^1-NMR)

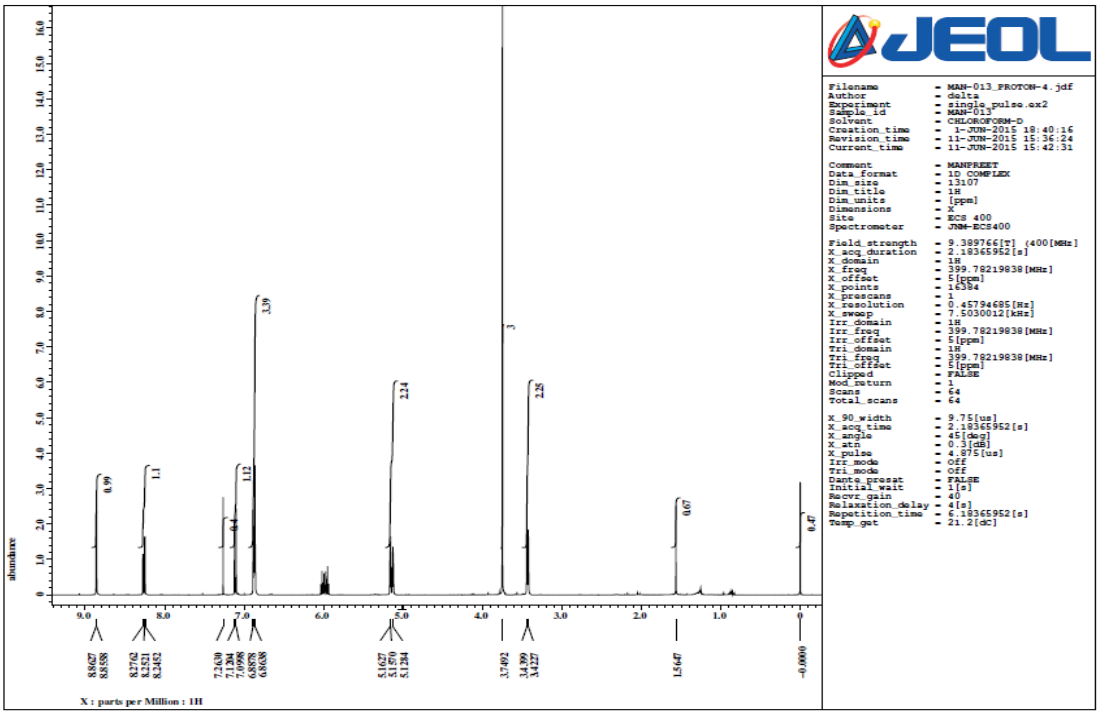


Figure 2a: Synthesis of Compound 2a (H^1-NMR)

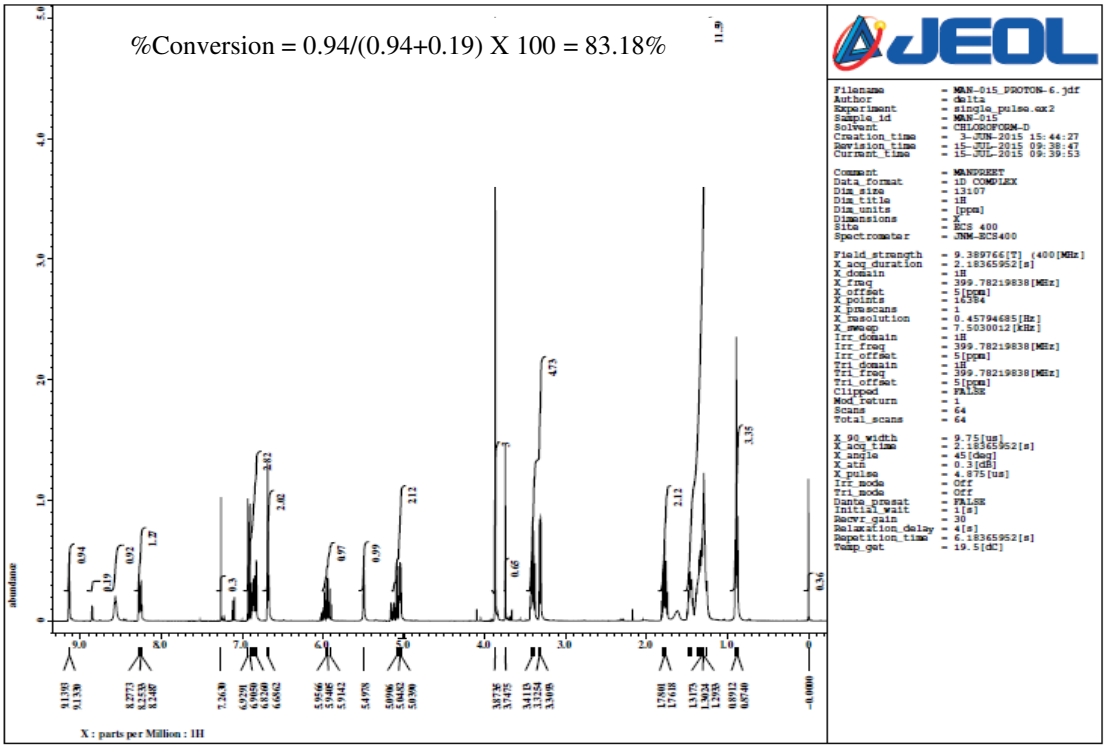


Figure 4: Deprotection of compound 2a Using Octyl Amine (H^1-NMR)

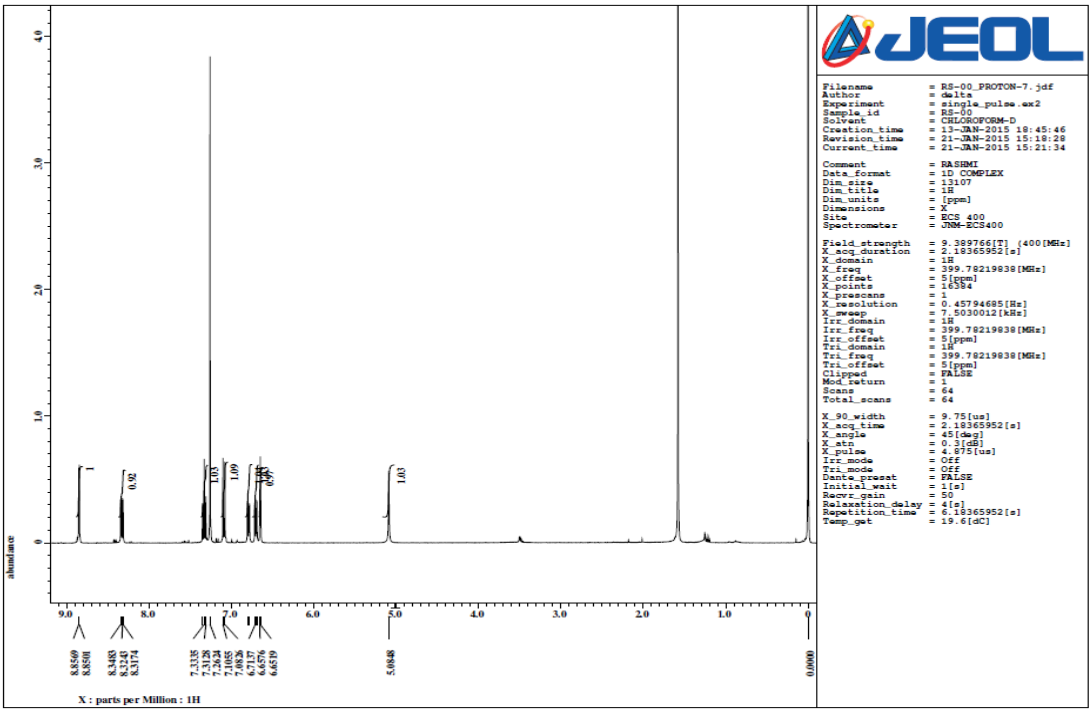


Figure 3a: Synthesis of Compound 3a (H^1-NMR)

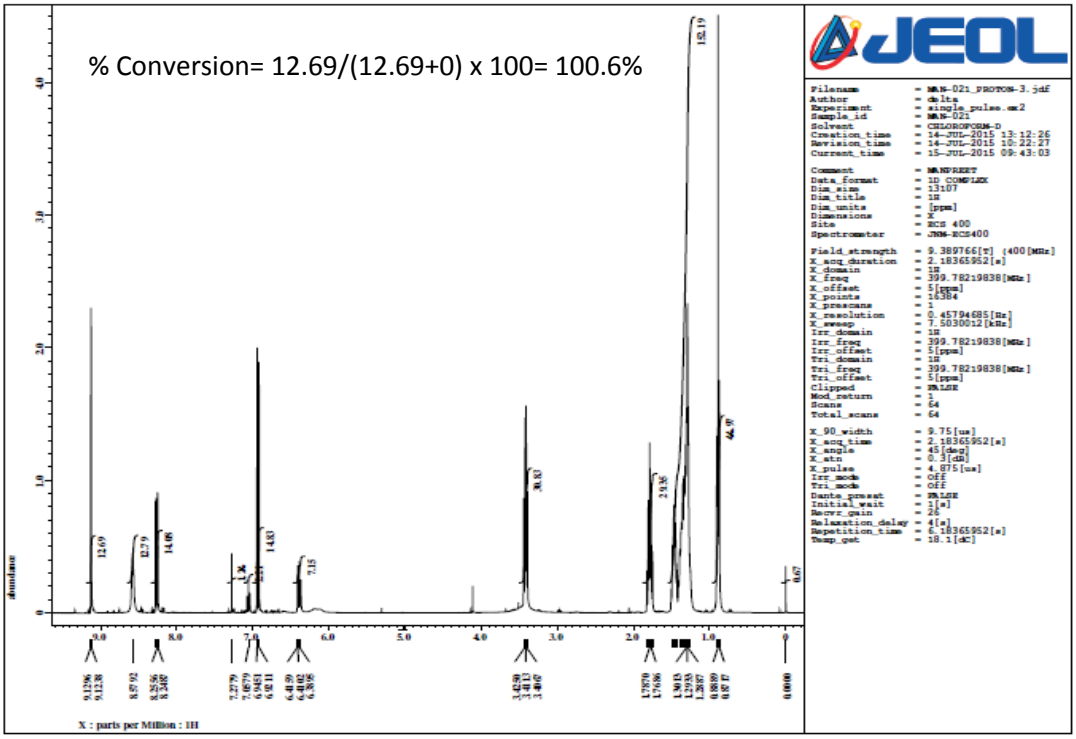


Figure 5: Deprotection of compound 3 Using Octyl Amine (H^1-NMR)

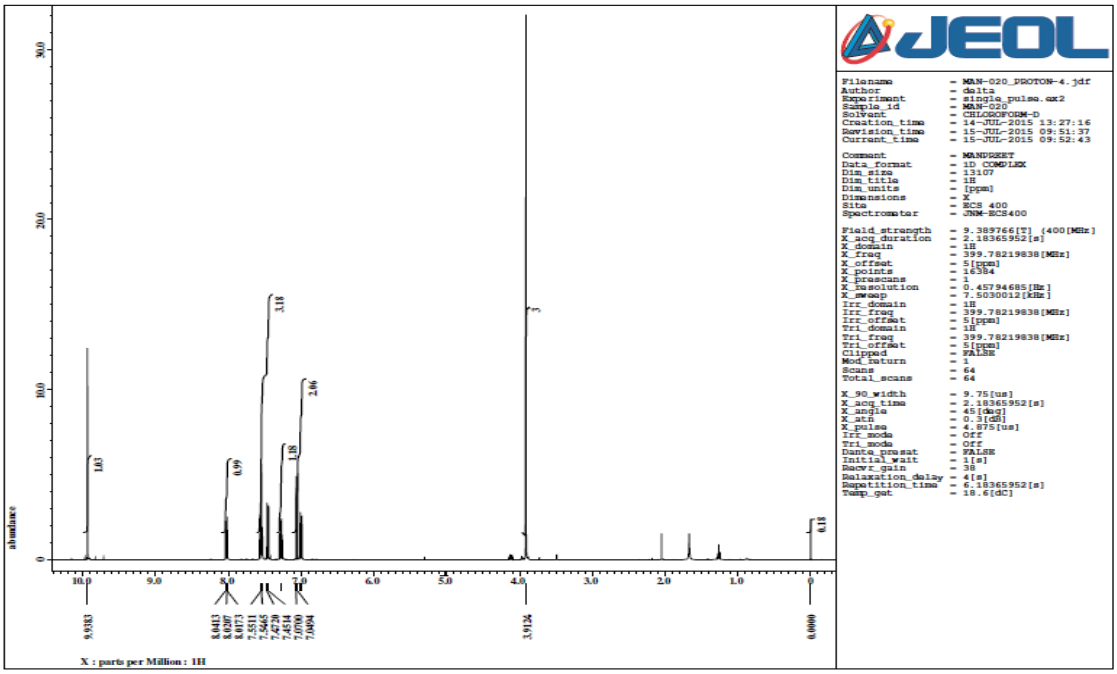


Figure 4a: Synthesis of Compound 4a

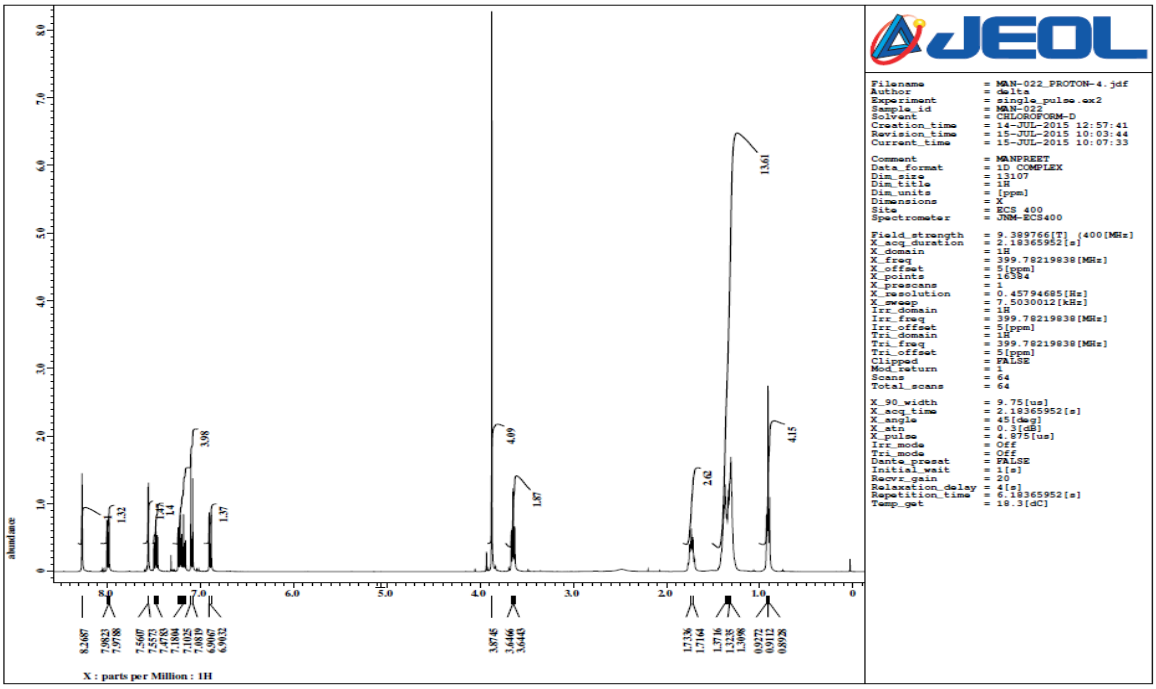


Figure 6: Schiff Base Formation of Compound 4a with Octyl Amine (H^1-NMR)

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